

# Biginelli Reaction: A Green Perspective

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**Abstract:** The Biginelli Reaction is a one-pot acid catalysed cyclocondensation of  $\beta$ -keto ester, urea and aromatic aldehyde which leads to the synthesis of functionalised 3,4-dihydro-2(*H*)-pyrimidinones (DHPMs). This three-component reaction for the synthesis of dihydropyrimidinone and corresponding dihydropyrimidinethiones has now been known for more than a century since first reported in 1893. Owing to the increasing use of Green technology approach, due to its various merits over Classical methodology and as a need for sustainable Chemistry, this reaction has received renewed interest for preparing DHPMs in an environmentally thoughtful manner with improved yields. The classical reaction has been modified in the recent past by using various catalysts and several structural variants in different solvents to synthesize large number of Biginelli type compounds. Also, these DHPMs (synthetic and natural) possess a wide range of pharmacological activities. We hereby wish to compile, in this present review, the literature available methods related to large number of Biginelli type compounds synthesized using eco-friendly technologies. This protocol couples the benefits of Biginelli reaction with that of greener approach for organic transformations, thus facilitating efficient synthesis of bioactive compounds in environmentally benign way.

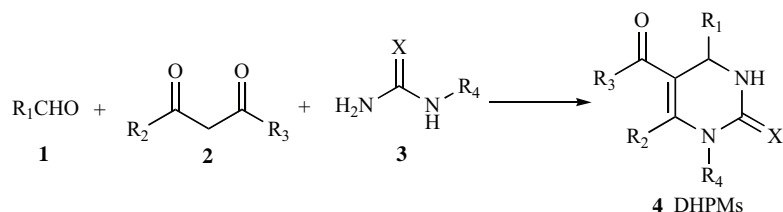
**Keywords:** Dihydropyrimidinone, dihydropyrimidinethione, multicomponent reactions, water, microwave, ionic liquid.

## 1. INTRODUCTION

Multicomponent reactions have apparently been a road to the synthesis of large number of compounds. They hold an upper hand over multistep synthesis owing to their efficiency, cost effectiveness, easy operation, high product complexity and large molecular diversity. Even though the idea is quite old, it is in recent decades that the multicomponent reaction is being recognized as a powerful weapon in the synthetic chemist's armoury and hence has attracted

The broad spectrum of biological functions that DHPMs possess has already been systematically reviewed by independent chemists [10, 11] and they have also been demonstrated as useful building blocks for the synthesis of versatile heterocyclic derivatives *via* postmodification (Scheme 2) [12-18].

Thus, it became inevitable that the Biginelli synthesis of DHPMs be pursued in an environmentally friendly manner for its perpetual use. During the past several decades, numerous methods



Scheme 1.

major attention [1-3]. A particularly representative application of these is in the rapid synthesis of structurally diversified molecular libraries, useful in discovering new pharmacophores [4-5].

One of the classical multicomponent strategies for synthesizing heterocycles is the Biginelli three-component condensation of an aldehyde (**1**), a  $\beta$ -keto ester (**2**) and a urea or thiourea (**3**) that affords a 3,4-dihydropyrimidin-2(1*H*)-(thi)one (**4**) (DHPM) (Scheme 1) [6]. The reaction continuously attracts research interest because of the occurrence of the DHPM moiety in various drug candidates, examples of which include the first cell-permeable antitumor scaffold, monastrol (**A**) [7], the modified analogue (*R*)-mon-97 (**B**) [8] and antihypertensive agent (*R*)-SQ 32,926 (**C**) [9] (Fig. 1).

have been developed for synthesizing DHPMs. Although a large number of new catalysts have been reported [19] to furnish DHPMs in an elegant manner and Kappe has comprehensively reviewed research progress on the Biginelli reaction during different time periods [20-21], there has been no dedicated compilation of the eco-friendly synthesis of DHPMs using this reaction. Therefore, we hereby review the synthesis of DHPMs using green methodologies other than the classical Biginelli protocol, in hope of providing a different perspective on DHPM synthesis. The review covers the application of greener protocols for Biginelli reactions using water, microwave, ionic liquids and other environmentally benign techniques.

## 2. SYNTHESIS OF DHPMS USING MICROWAVE

Chemical reactions are better managed thermally by the use of Microwave irradiation as it facilitates rapid heat transfer which

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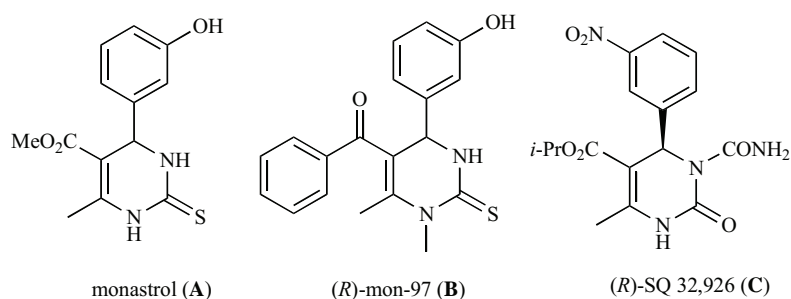
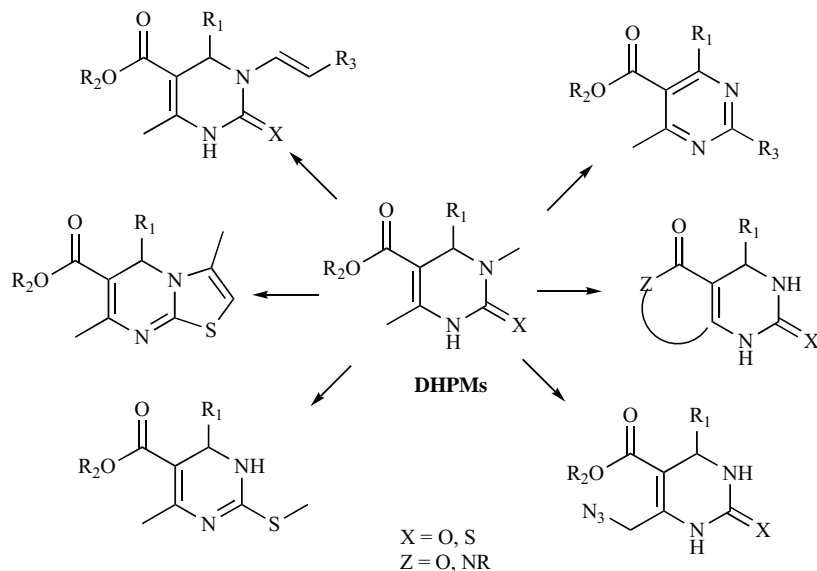
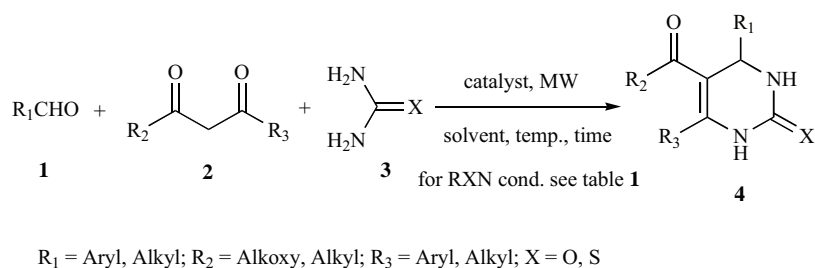


Fig. (1).



Scheme 2.



Scheme 3.

allows reactions to be carried out very much faster compared to conventional heating methods often resulting in increased product yield with lower energy usage. Furthermore, the products of temperature sensitive reactions can be selectively controlled and tuned as the conditions are milder than classical methods.

Due to the shorter reaction duration and the number of organic reactions covered by microwave assisted synthesis, it has emerged as a crucial technique for the pharmaceutical industry which is always in need of new compounds.

Thus, for developing a safe, simple, eco-friendly and economic strategy for sustainable use, microwave irradiation has been extensively used and studied [22] for the synthesis of DHPMs by Biginelli multicomponent synthesis in the presence or absence of a solvent (Scheme 3), as tabulated below (Table 1).

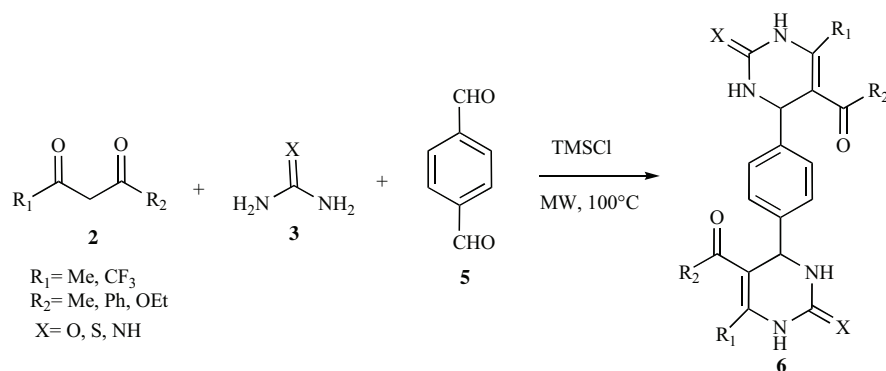
Besides these, there have been reports of other variants in Biginelli reaction methodology under microwave irradiation by replacing the active methylene compounds (usually ethylacetoacetate), urea/thiourea or the aldehyde, to yield a variety of Biginelli like products. The simplest variation is of the aromatic aldehyde, as given by Azizian *et al.*, by a di-aldehyde (5) to give bis-DHPMs (6) (Scheme 4) [61].

El-Rahman *et al.* (Scheme 5) [62] and Naik *et al.* (Scheme 6) [63], have similarly reported reactions using heterocyclic aldehydes giving respectively substituted DHPMs.

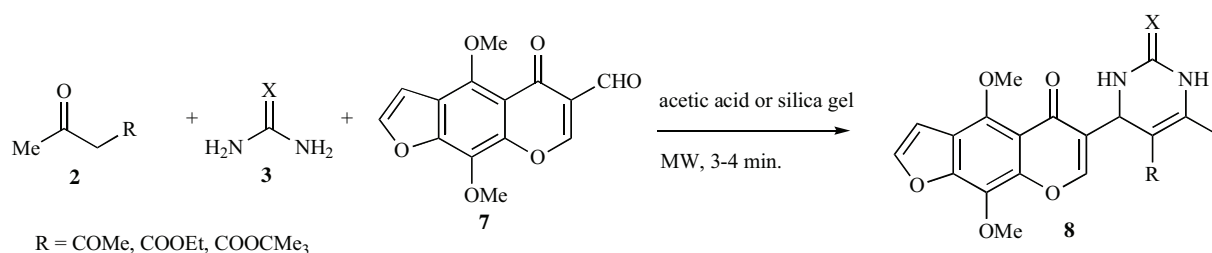
Yadav *et al.* have envisaged diastereoselective synthesis of thiosugar-annulated multifunctionalized utilised monosaccharides as aldehyde variants with different alternative  $\beta$ -dicarbonyl compounds, 2-methyl-2-phenyl-1,3-oxathiolan-5-one (12) (at 90°C for

Table 1. Synthesis of DHPMs Under Microwave Irradiation

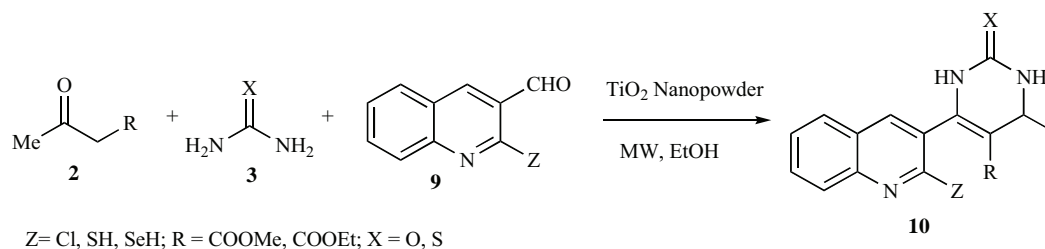
S. No.	Solvent	Catalyst	Temp. (°C), (Power)	Time (min)	Ref.
1.	Ethanol	Cu(OTf) <sub>2</sub>	100 (200W)	60	[23]
2.	Neat	5-sulphosalicylic acid	NA (350W)	1.5-4	[24]
3.	Neat	Ni NPs (8 mol %)	NA (360W)	3-7	[25]
4.	Neat	AlCl <sub>3</sub> .6H <sub>2</sub> O (10 mol %)	NA (220W)	1.5-3	[26]
5.	Ethanol	HCl (20 mol %) HCl (37%) HCl (1-2 drops)	120(600W) (50%) (360 W)	20 25-50s 4-11	[27, 28, [29]
6.	Neat	I <sub>2</sub>	60 (600W)	15	[30]
7.	Neat	VOSO <sub>4</sub> (5 mol %)	NA (360W)	2-5	[31]
8.	Neat	Al(H <sub>2</sub> PO <sub>4</sub> ) <sub>3</sub> (31 mol %)	NA (300W)	10-20	[32]
9.	Neat	Al <sub>2</sub> O <sub>3</sub> -SO <sub>3</sub> H	NA (180W)	1.5-3	[33]
10.	Neat	--	130 (10W)	18	[34]
11.	Water	Polystyrenesulfonic acid	80 (40–100 W)	20	[35]
12.	Neat	HClO <sub>4</sub>	NA (1200W)	0.5-5	[36]
13.	Neat	Phosphotungstic acid/sulphated zirconia	NA	1.5-2	[37]
14.	Neat	Activated fly ash	90 (160W)	2-3	[38]
15.	Neat	ZrO <sub>2</sub> -pillared ZrO <sub>2</sub> -nanopowder	NA(630W) 53-65 (320W)	4-7 0.5-1	[39, 40]
16.	Neat	SnCl <sub>2</sub> .H <sub>2</sub> O/ SnI <sub>2</sub>	NA (60% of 800W)	3	[41]
17.	Neat	PEG-SO <sub>3</sub> H	100()	6	[42]
18.	Na <sub>2</sub> SO <sub>4</sub>	In(OTf) <sub>3</sub> (2 mol%)	NA ( 30%)	8-15	[43]
19.	Neat or Al <sub>2</sub> O <sub>3</sub>	--	110-120(800W)	1.5-10.5	[44]
20.	Neat	FeCl <sub>3</sub> .6H <sub>2</sub> O	(180 W)	15	[45]
21.	Neat	--	140(400W)	12-16	[46]
22.	Ethanol	Trichloroisocyanuric acid(15 mol% )	(600 W)	3	[47]
23.	Neat	Bi(NO <sub>3</sub> ) <sub>3</sub> (2 mol%)	100 (300 W)	4.5-5	[48]
24.	Neat	HCOOH	(120 W)	3-8	[49]
25.	Al <sub>2</sub> O <sub>3</sub>	SbCl <sub>3</sub> (5 mol%)	(5 power level)	1-2.5	[50]
26.	MeCN	Yb(OTf) <sub>3</sub> (10 mol%)	120 ( 0-1400W)	20	[51]
27.	Neat	<i>p</i> -TSA	(150 W)	5	[52]
28.	Neat	CuSO <sub>4</sub> .5H <sub>2</sub> O (1 mol%)	(60%)	1-2	[53]
29.	K10 clay	FeCl <sub>3</sub>	(700W)	3-5	[54]
30.	Neat	PPE	(900W) (50% 800W)	3 3-3.5	[55, 56]
31.	Neat	PEG 4000	(400W)	1.5-2.5	[57]
32.	Neat	--	--	1-5.7	[58]
33.	DMF	TMSCl and Co(OAc) <sub>2</sub> .4H <sub>2</sub> O	300W	7	[59]
34.	Neat	[Hmim]HSO <sub>4</sub>	130 W	1-5	[60]



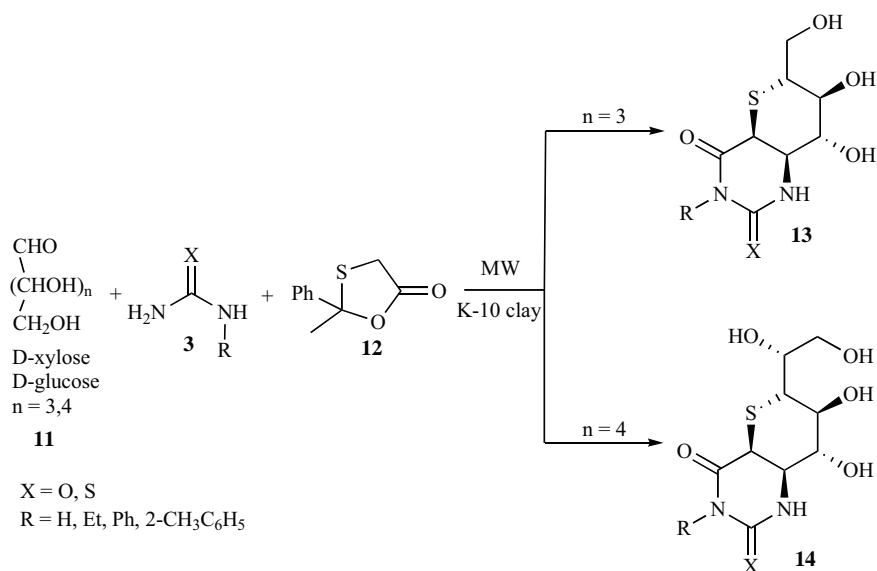
Scheme 4.



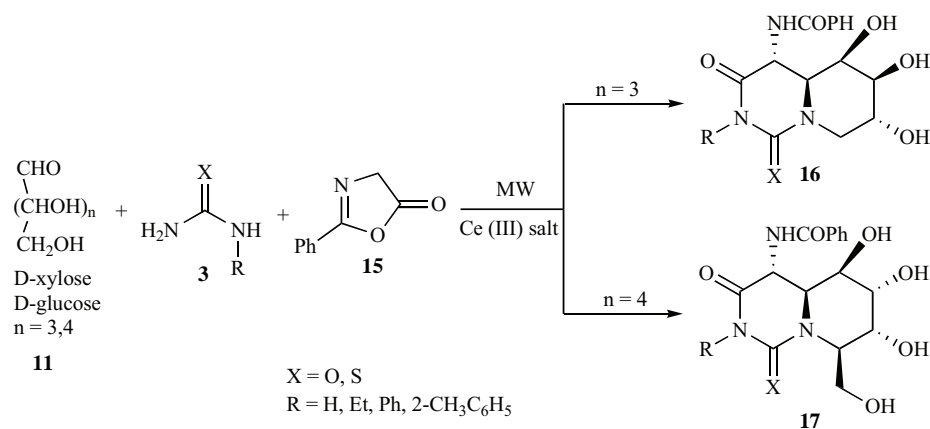
Scheme 5.



Scheme 6.



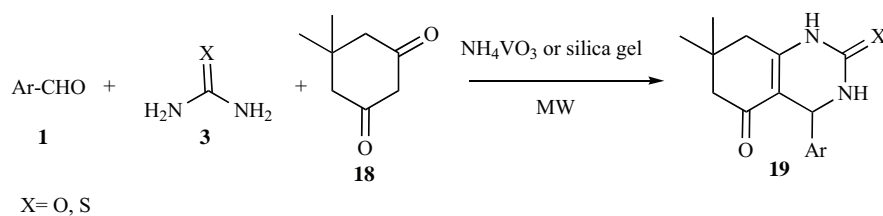
Scheme 7.



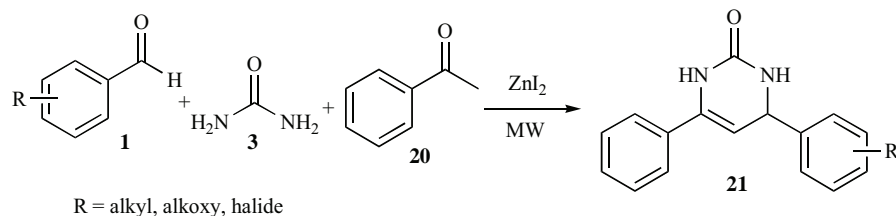
Scheme 8.

5-13 min) using Montmorillonite K-10 clay (Scheme 7) [64] and 2-phenyl-1,3-oxazol-5-one (15) in presence of Ce<sup>3+</sup> (at 90°C for 4-13 min) (Scheme 8) [65].

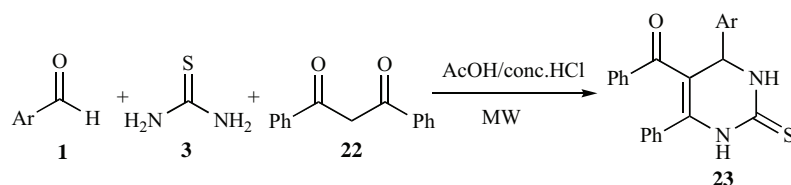
Also, enroute to DHPMs using microwave irradiation a few octahydroquinazolinone derivatives (19) have also been reported by Nirahwad *et al.*, using cyclic 1,3-diketones (18) and NH<sub>4</sub>VO<sub>3</sub> (5 and



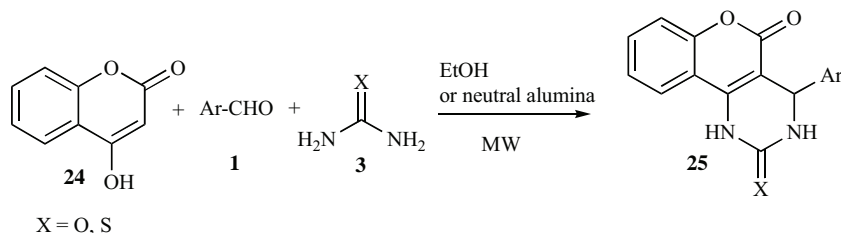
Scheme 9.



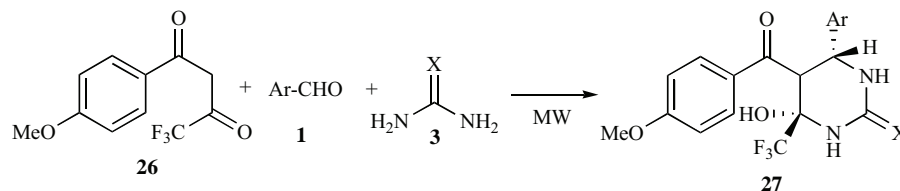
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

7 mol%) [66] (found as the best in comparison to  $\text{KH}_2\text{PO}_4$ , Alum, acidic alumina, sulfamic acid, amberlite and cellulose sulphuric acid with best results at 360 W power), for 5-12 minutes irradiation. These have been earlier reported by using microwave irradiation on silica gel TLC plates at 95-105°C and power of 560 W for 2-3.2 minutes, at an interval of 40 seconds intermittently (Scheme 9) [67].

Acetophenone (20) ( $\text{ZnI}_2$  (20% molar), 75-750W, 5-10 min) [68] (Scheme 10) and 1,3-diphenyl-1,3-propanedione (22) ( $\text{AcOH/conc.HCl}$ , 700W, 5 min.) [69] (Scheme 11) have also been reported as a modification of active methylenes for Biginelli synthesis of DHPMs.

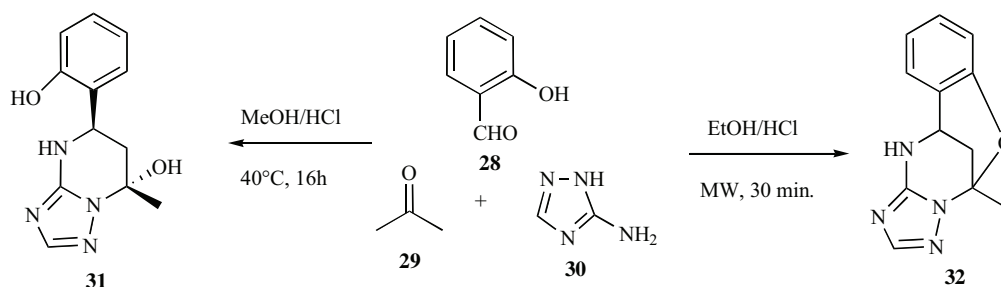
In a similar manner, 4-hydroxycoumarin (24) (neutral alumina/ $\text{EtOH}$ , 90-110°C, 800W, 4.5-7.1 min) [70] (Scheme 12) and 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione (26) (110-120°C, 600W, 1.5-6.5min.) [71] (Scheme 13), also give fused DHPMs and tetrahydropyrimidinones respectively.

Gorobets *et al.* have given another variation of the urea/thiourea moiety by 3-amino-1,2,4-triazole (30) in a Biginelli-like three-component condensation with different salicylic aldehydes (28) and acetone (29). The use of salicylic aldehydes gives different products under classical ( $\text{MeOH/HCl}$ , 40°C, 16h) and microwave irradiation ( $\text{EtOH/HCl}$ , 300W, 150°C, 30 min.) (Scheme 14) [72].

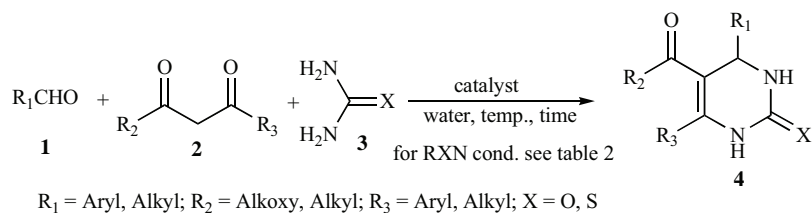
### 3. SYNTHESIS OF DHPMs USING WATER AS SOLVENT

Use of water as the reaction medium offers several advantages:

- (i). easy availability, zero cost, nonflammable, non-toxic and safe for use;
- (ii). elimination of the additional efforts required to make the substrates or reagents dry before use and thereby reducing the consumption of drying agents, energy and time;
- (iii). increased reactivity or selectivity owing to its unique physical and chemical properties [73]; and easy isolation.



Scheme 14.



Scheme 15.

Table 2. Synthesis of DHPMs in Water Medium

S.No.	Catalyst	Temp. (°C)	Time (h)	Ref.
1.	Thiamine hydrochloride(Vit B1)	Ultrasonic	15-25min	[76]
2.	MgSO <sub>4</sub> (10 mol%)	90	4-8	[77]
3.	Aq. Zn(BF <sub>4</sub> ) <sub>2</sub> (40% w/v)	r.t	3	[78]
4.	Polystyrenesulfonic acid	80	20	[79]
5.	CuCl <sub>2</sub> ·2H <sub>2</sub> O (10 mol %) Sodium dodecylsulfonate (20 mol %)	60	24	[80]
6.	M(NTf <sub>2</sub> ) <sub>n</sub> or M(OTf) <sub>n</sub> (5 mol%, M=Cu, Yb, Ni, Zn)/(CH <sub>3</sub> COOH/ CF <sub>3</sub> COOH)	r.t	24	[81]
7.	-	-	5min	[82]
8.	Ag <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (10% w/w of aldehyde)	80	3-4.5	[83]
9.	CeCl <sub>3</sub> ·7H <sub>2</sub> O (10 mol %)	90	10	[84]
10.	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub> (30 mol%)	55-60	3-4.5	[85]
11.	CuI (15 mol%)	90	4-6	[86]
12.	Montmorillonite KSF	100	10	[87]
13.	Amberlyst-70	90	3	[88]

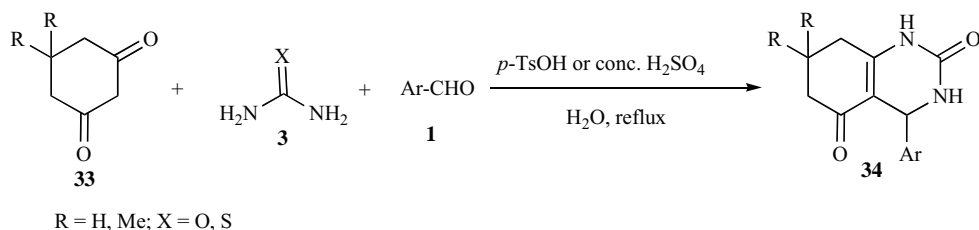
tion of products by filtration. This has inspired the chemist to use aqueous medium in an exhaustive manner [74,75].

Being a universal solvent, water acts as a best solvent among all the green solvents possible. As it can activate both electrophiles and nucleophiles, hence it accelerates polar reactions. With increase in attention for greener approaches for organic synthesis, the use of water in Biginelli reactions for the synthesis of dihydropyrimidinones has also been explored in the recent past. By denying the use of any organic solvent and toxic metals as catalyst, minimizing the cost, the operational hazards, and environmental pollution, it provides an eco-friendly synthesis of these moieties. Also, this modified route provides much higher yields and simple work-up procedure of products. Table 2 lists the reactions using water as a solvent to obtain DHPMs (Scheme 15).

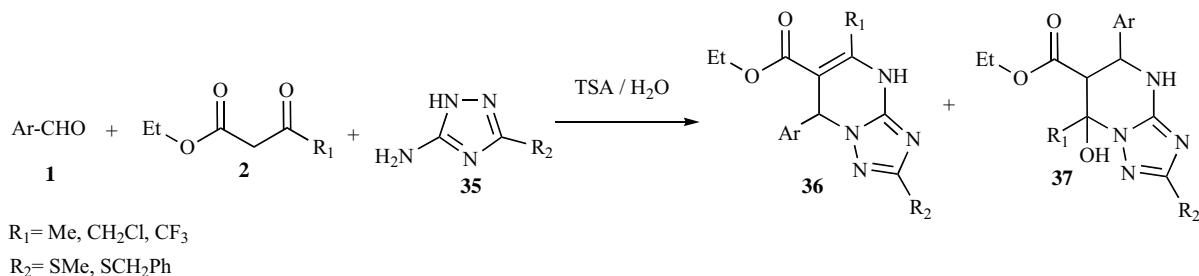
Apart from the above procedures (for Scheme 15) using water as solvent, synthesis of octahydroquinazolinone derivatives (34) has

also been reported by Biginelli-type three-component cyclocondensation reactions using cyclic 1,3-diketones (33) and *p*-TsOH [89] or conc. H<sub>2</sub>SO<sub>4</sub> [90] as catalysts in water (Scheme 16). Based on the reaction yields and environmental consideration, water was proved to be the best solvent among the other solvents such as acetonitrile, ethanol and toluene.

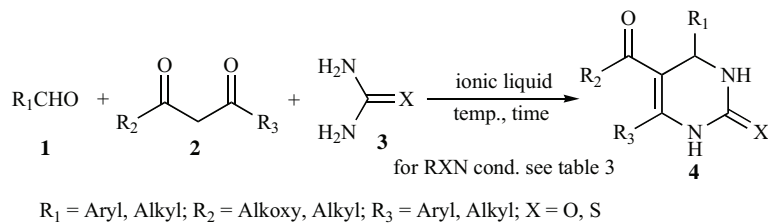
Another set of differently substituted fused DHPMs, dihydrotriazolo-pyrimidine (36), [91] have been synthesised by Chen *et al.* through Biginelli reaction in water by replacing the urea component with 5-amino-1,2,4-triazole (35) (Scheme 17). Ethyl trifluoroacetate (2), when used as  $\beta$ -ketoester, showed regioselectivity of the aminotriazole on the basis of aldehyde used. The conventional heating required was for 10h at 80°C using TSA as a catalyst in water while microwave irradiation improved the yields of the reaction in C<sub>2</sub>H<sub>5</sub>OH solution with 37% HCl as catalyst and shortened the reaction time to a great extent.



Scheme 16.



Scheme 17.



Scheme 18.

#### 4. SYNTHESIS OF DHPMs USING IONIC LIQUIDS

Ionic liquids (ILs) have attracted increasing interest in the context of green chemistry owing to their great potential as environmentally benign reaction media. They are defined as organic cations and inorganic or organic anions. An important class of non-aqueous ionic liquids belongs to the imidazolium-based salts. There are many advantages of ionic liquids over conventional solvents as they have:

- no significant vapor pressure, and hence cannot emit volatile organic compounds [92].
- high thermal stability [93].
- low solubility of organic compounds in some types of ionic liquids will make separation of products easy.
- solvophobic interactions in the reaction mixture, generate an internal pressure which promote the association of the reagents in a solvent cavity during the activation process and accelerate the reactions in comparison to conventional solvents [94].
- the utility of being recyclable [95].

Table 3. below enlists the reactions using ionic liquids as a catalyst to obtain DHPMs (Scheme 18).

Apart from the above, another green protocol for the Biginelli reaction starting from alcohols (38) instead of aldehydes has been reported [107]. It involves 1-methylimidazolium hydrogen sulphate, [Hmim]HSO<sub>4</sub>, catalyzed *in situ* oxidation of aromatic alcohols to aromatic aldehydes with NaNO<sub>3</sub> followed by their cyclocondensa-

tion with 1,3-dicarbonyl compounds (2) and urea (3) to obtain 3,4-dihydropyrimidin-2-(1*H*)-ones (4) (Scheme 19).

Besides this, chiral ionic liquids, [108] L-prolinium sulfate (Pro<sub>2</sub>SO<sub>4</sub>), L-alaninium hexafluorophosphate (AlaPF<sub>6</sub>) and L-threoninium nitrate (ThrNO<sub>3</sub>), obtainable from a natural α-amino acid, have been used in the Biginelli reaction. Asymmetric induction and thus enantio- and diastereomerically pure perhydropyrimidines (39, 40) have been synthesised using variants (2-phenyl-1,3-oxazol-5-one (15) or 2-methyl-2-phenyl-1,3-oxathiolan-5-one (12)) of β-ketoesters (Scheme 20).

#### 5. SYNTHESIS OF DHPMs USING ETHANOL AS SOLVENT

The growing concern for the environment demands the development of eco-friendly and economic processes. Replacement of conventional, toxic and polluting solvent with eco-friendly solvent like ethanol as reaction medium (Scheme 21) is also considered as an eco-friendly method for the synthesis of DHPMs (Table 4).

In addition to these, Zhang *et al.* reported the synthesis of 4-substituted pyrazolyl-3,4-dihydropyrimidin-2(1*H*)-(thio)ones (42) by Biginelli condensation reaction of 5-chloro/phenoxy-3-methyl-1-phenyl-4-formylpyrazole (41), 1,3-dicarbonyl compound (2) and urea or thiourea (3) using Mg(ClO<sub>4</sub>)<sub>2</sub> as a catalyst in ethanol under refluxing conditions (Scheme 22) [115].

Lin *et al.* has reported the use of Nafion-H as catalyst to achieve the synthesis of octahydroquinazolinone derivatives (34) by following Biginelli-type reaction (Scheme 23) [116].

**Table 3. Synthesis of DHPMs in Ionic Liquids**

S.No.	Ionic Liquid	Temp. (°C)	Time (Min)	Ref.
1.	TSILs (2 mol%)	90	10	[93]
2.	[Hmim]HSO <sub>4</sub>	90	10-25	[60]
3.	[Hmim] [FeSO] (10 mol%)	90	2-3 h	[96]
4.	[Hmim]HSO <sub>4</sub>	80-85	15-55	[97]
5.	HSO <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> COOHmim]HSO <sub>4</sub>	75	0.5-1.5	[95]
6.	TSILs (2 mol%)	90	10-15	[98]
7.	[Hmim]BF <sub>4</sub> (1mL) & Cu(acac) <sub>2</sub> (5 mol%)	50	15	[99]
8.	[HOC <sub>2</sub> mim][PF <sub>6</sub> ], HCl (0.5 mol%)	100	30	[100]
9.	TMGT	100	5-50	[101]
10.	[bmim]Cl.2AlCl <sub>3</sub>	r.t	45-90	[102]
11.	[Hbim] BF <sub>4</sub>	30-31, ultrasonic (120W)	45	[103]
12.	IL-OPPh <sub>2</sub>	100	1.3-3.5h	[104]
13.	CMImHSO <sub>4</sub> (5 mol%)	80	15	[105]
14.	BMImBF <sub>4</sub> or BMImPF <sub>6</sub>	100	30	[106]

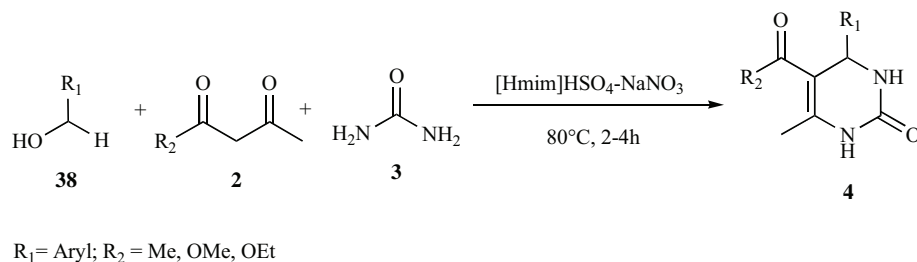
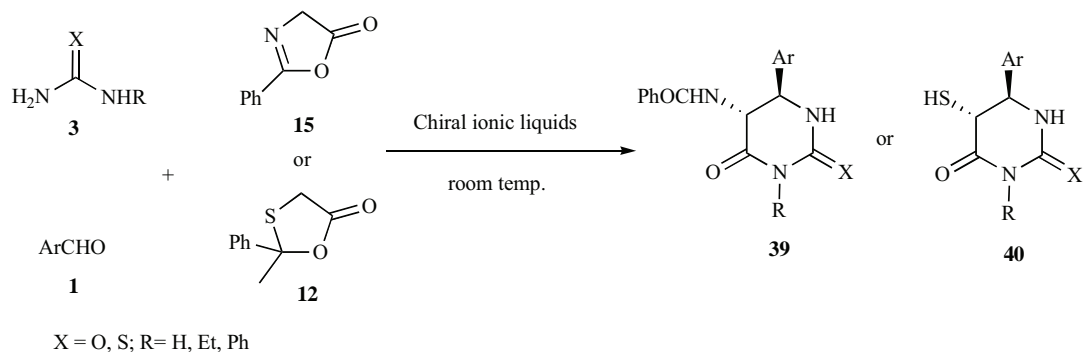
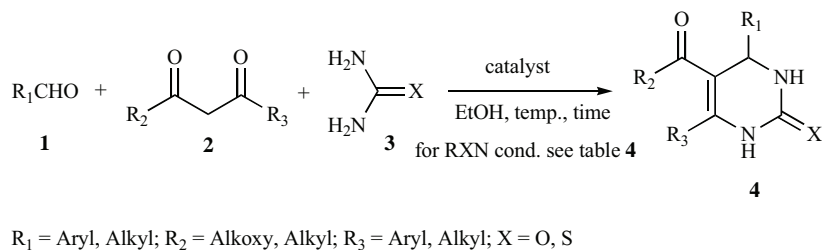
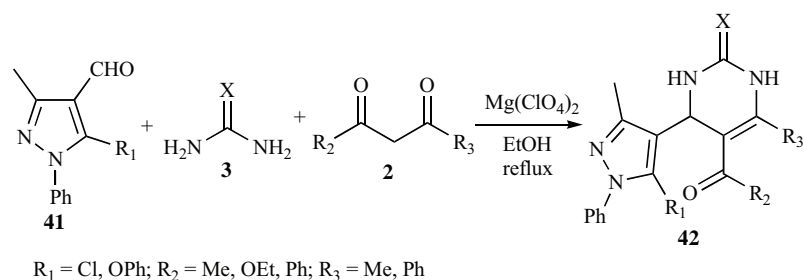
**Scheme 19.****Scheme 20.****Scheme 21.**

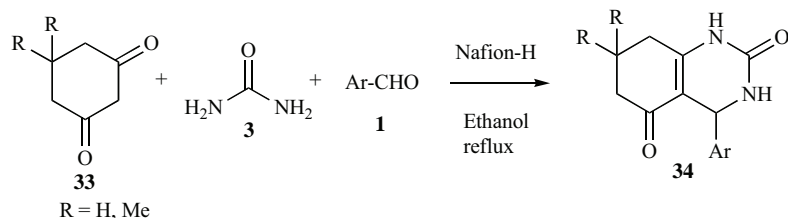


Table 4. Synthesis of DHPMs in Ethanol

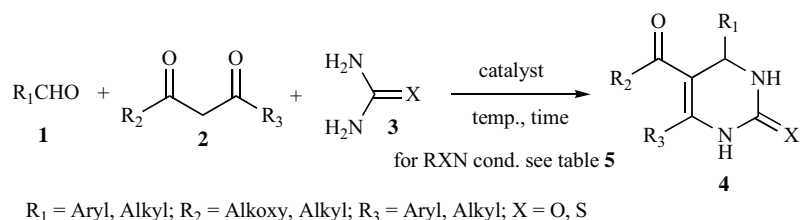
S. No.	Catalyst	Condition	Time (h)	Ref.
1.	Cellulose sulphuric acid	reflux	2-4	[109]
2.	Polystyrene-supported $\text{AlCl}_3$	reflux	6	[110]
3.	Nafion-H (100 wt. %)	reflux	4	[111]
4.	$\text{CaCl}_2$	reflux	2-6	[112]
5.	Zeolite	$80^\circ\text{C}$	2-8	[113]
6.	Indium(III) bromide (10 mol %)	reflux	0.5-7	[114]



Scheme 22.



Scheme 23.



Scheme 24.

## 6. SYNTHESIS OF DHPMs UNDER SOLVENT FREE CONDITION

Besides the above green methodologies, DHPMs were also prepared under solvent free conditions with or without use of non-toxic and reusable catalyst (Scheme 24). The list of such type of reactions is enlisted in Table 5.

Furthermore, another procedure employed by Al-Kadasi *et al.* [143] involved the condensation of benzaldehydes, diketone/ $\beta$ -ketoester with urea/thiourea, using sonicator irradiation, at ambient temperature promoted by chlorosulphonic acid ( $\text{ClSO}_3\text{H}$ ) under solvent-free condition to afford 3,4-dihydropyrimidin-2(1H)-ones.

Alizadeh and Rostamnia recently published a route to 3,4-dihydropyrimidin-2(1H)-one derivatives (45) under solvent free conditions by Biginelli-type condensation [144]. This protocol involves the condensation of adduct diketene (43), MeOH/EtOH,

benzaldehyde (1), urea (3) in TFA (10 mol%) under refluxing conditions for 10 min to yield the desired product (Scheme 25).

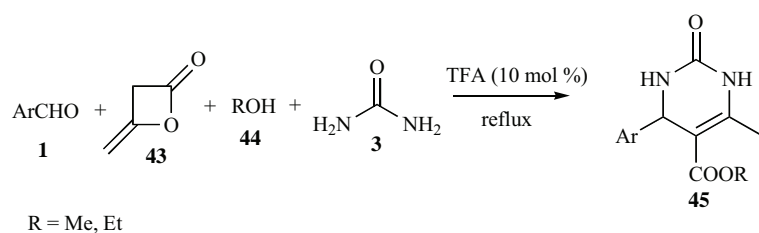
Lei *et al.* and Zhang *et al.* have reported a range of pyrimidinone derivatives (Biginelli-type product) synthesized by condensing two moles of aldehyde (1) with one mole of cyclopentanone (46) and urea or thiourea (3) at  $140^\circ\text{C}$  [145] as well as at  $90^\circ\text{C}$  with  $\text{YbCl}_3$  (3 mol %) as catalyst [146] under solvent free conditions, respectively (Scheme 26).

Shobha *et al.* have reported the efficient Biginelli one-pot synthesis of new benzoxazole substituted dihydropyrimidinones and thiones (49) under solvent free conditions using trifluoro acetic acid [147]. A similar synthesis by Arjun *et al.* uses alumina-supported trifluoromethane sulfonic acid [148] as catalyst (Scheme 27).

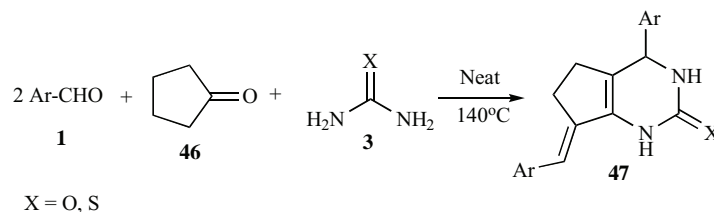
4,6-Diarylpyrimidin-2(1H)-ones (21) were prepared by Khosropour *et al.* by condensation of arylaldehyde (1), aryl methyl ke-

Table 5. Synthesis of DHPMs Under Solvent Free Condition

S.No.	Catalyst	Temp. (°C)	Time	Ref.
1.	Calcium sulphate dehydrate (15 mol%)	100	1.5-2h	[117]
2.	$\beta$ -cyclodextrine-SO <sub>3</sub> H	100	1h	[118]
3.	Na <sub>2</sub> B <sub>4</sub> O <sub>7</sub> ·10H <sub>2</sub> O (5 mol%)	80	1-2	[119]
4.	Cu(NO <sub>3</sub> ) <sub>2</sub> ·3H <sub>2</sub> O (5 mol%)	70	25 min.-8h	[120]
5.	Al(HSO <sub>4</sub> ) <sub>3</sub> (10 mol%)	100	10-15 min.	[121]
6.	Al <sub>2</sub> O <sub>3</sub> -SO <sub>3</sub> H (15 mol%)	120	0.6-3.3h	[121]
7.	Na <sub>2</sub> H <sub>2</sub> PO <sub>4</sub>	80	30 min.	[122]
8.	Yb(OTf) <sub>3</sub>	120	3h	[123]
9.	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub> (30% w/w)	85	2h	[124]
10.	Titanium silicate (10 wt%)	50	10-35 min.	[125]
11.	Cu(TFA) <sub>2</sub> ·4H <sub>2</sub> O	60	4	[126]
12.	CuCl <sub>2</sub> ·2H <sub>2</sub> O (20 mol%)	100	20 min.-1h	[127]
13.	Tungstate Sulfuric Acid	Rt	10 min.	[128]
14.	CuCl <sub>2</sub> ·2H <sub>2</sub> O-conc. HCl	Grindstone Chemistry	2-5 min.	[129]
15.	Fe(CF <sub>3</sub> CO <sub>2</sub> ) <sub>3</sub> or Fe(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub> (5 mol%)	70	15 min.-3h	[130]
16.	Bi(NO <sub>3</sub> ) <sub>3</sub> ·5H <sub>2</sub> O	100	10 min.-3h	[131]
17.	PEG400-KH <sub>2</sub> PO <sub>4</sub>	110	1.5-7h	[132]
18.	ZrOCl <sub>2</sub> ·8H <sub>2</sub> O (10 mol %)	100	0.5-3h	[133]
19.	PEG400	100	45 min.	[134]
20.	Chloroacetic acid (10 mol%)	90	3h	[135]
21.	MgBr <sub>2</sub>	100	45-90 min.	[136]
22.	<i>p</i> -toluenesulfonic acid	Grindstone Chemistry	4-15 min.	[137]
23.	<i>N</i> -Butyl- <i>N,N</i> -dimethyl- $\gamma$ -phenylethylammonium bromide	100	20-60 min.	[138]
24.	Yb(OTf) <sub>3</sub> (5 mol%)	100	60-90min.	[139]
25.	NH <sub>4</sub> Cl	100	3h	[140]
26.	--	100-105	1h	[141]
27.	Yb(III)-resin	120	48h	[142]



Scheme 25.

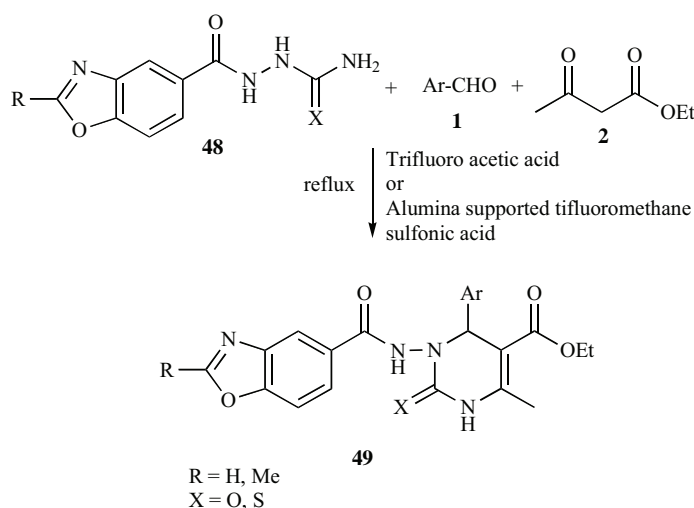


Scheme 26.

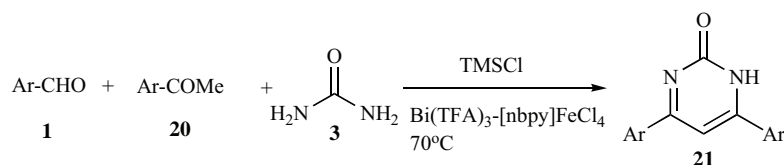
tone (**20**) and urea (**3**) in presence of trimethylsilyl chloride and bismuth(III) trifluoroacetate immobilized on [nbpy]FeCl<sub>4</sub> as low toxic catalyst (Scheme **28**) [149].

## 7. CONCLUSION

The environmental and economic perspectives, besides the urgency of finding new molecules in quick time, are making it obvi-



Scheme 27.



Scheme 28.

ous to change the traditional unsustainable methods of chemical synthesis. Owing to vast interest in the Biginelli reaction, it has acted as a viable medium for the comparison of classical methodologies and greener ways.

Microwave technology has been proved to be useful in saving time and improving yields in the Biginelli reaction besides the conversion of reactants into products which are different from classical ways. Hence, it can be claimed that energy utilisation in case of MW irradiated reactions is in somewhat different manner than the usual. Also, in case of MW irradiation a number of variations in the catalyst, MW power and time of reaction have been observed to find out the most suitable combination for getting higher yields.

Similarly, water, ionic liquids and ethanol have been found to be clinical as solvents for Biginelli reaction. Whereas, water provides the facility of easy separation without drying conditions or use of PTC being required, ethanol gives the range of polarity for the reactants solubility. In case of Ionic Liquids, they have been vastly used for Biginelli reaction with a special emphasis on their recyclability in some cases.

The reactions achieved by just mixing the reactants without any media called as solvent free conditions have also been pretty useful for Biginelli reaction in an eco-benign manner.

Thus, it can be concluded from the above that conducting Biginelli reaction in an environmentally friendly manner in more than one ways has been found to be economical apart from protecting the environment.

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